Practitioner's Docket No. MPI96-027CP2RCE2M

REMARKS

Claim 200 has been amended. No new matter has been added by way of amendment. Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 will be pending upon entry of the instant amendment.

NEW REJECTIONS

The Rejection of Claims 200, 202-205, and 208 under 35 U.S.C. §112, First Paragraph, (Written Description) Should Be Withdrawn

The Examiner rejected claims 200, 202-205, and 208 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner stated,

> "Claim 200, from which each of claims 202-205 and 208 depends, is drawn to a kit which comprises, 'one or more ancillary reagents suitable for detecting the presence of a complex...'. The specification fails to disclose the structure of those ancillary reagents..."

Applicants traverse the rejection. However, in an effort to expedite prosecution, Applicants have amended claim 200 to delete recitation of "ancillary reagents", thus rendering the rejection moot.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims 200, 202-205, and 208 under 35 U.S.C. 112, first paragraph.

The Rejection of Claims 158, 160, 179, 181, 200 and 202 under 35 U.S.C. §102(a) Should Be Withdrawn

The Examiner rejected claims 158, 160, 179, 181, 200 and 202 under 35 U.S.C. §102(a) as being anticipated by Bleul (March 1997, PNAS 94:1925-1930), as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997. Specifically, the Examiner stated,

> "Bluel [sic] discloses monoclonal antibody 5C7, raised against CCR5; see p. 1925 final paragraph. While the reference is silent as to whether the antibody binds to the second extracellular loop of CCR5, as recited in claim 158, this is an inherent property of the antibody. The instant specification discloses (p. 3 line 17- p. 4 line 4) that antibody 5C7 is has these properties. Thus the antibody disclosed by Bluel has all the functions recited in claim 158."

Applicants traverse the rejection. Applicants submit that, as outlined below, the 5C7 antibody disclosed by Bleul et al. does not possess all the limitations of the claimed antibodies, and therefore cannot anticipate the claimed antibodies.

The Examiner's characterization of the antibody 5C7 is factually incorrect. The Examiner states that Bleul et al. is silent as to whether 5C7 binds to the second extracellular loop of CCR5, but argues that such is an inherent property of 5C7, and that the instant specification discloses (at pages 3-4) that 5C7 binds the second extracellular loop. Antibody 5C7 does not bind the second extracellular loop of CCR5, and does not inhibit binding of chemokine ligands to CCR5, as detailed below.

As a preliminary matter, Applicants point out that pages 3-4 of the instant specification do not disclose that 5C7 binds the second extracellular loop of CCR5 (see p. 3 line 17- p. 4 line 4, reprinted below). The cited section describes that in one embodiment, the antibody is monoclonal antibody 5C7, or a monoclonal antibody which can compete with 5C7. The section of the specification cited by the Examiner is silent as to any characteristics of the 5C7 antibody.

> "The present invention relates to an antibody (immunoglobulin) or functional portion thereof (e.g., antigen binding fragment) which binds to a mammalian chemokine receptor 5 protein (also referred to as CKR-5 or CCR5) or portion of the receptor (anti-CCR5). In one embodiment, the antibody of the present invention has specificity for human CCR5 or portion thereof, wherein the antibody blocks binding of a ligand (e.g., RANTES, MIP-1α, MIP-1β, human immunodeficiency virus (HIV)) to the receptor and inhibits function associated with binding of the ligand to the receptor (e.g., leukocyte trafficking). For example, as described herein, antibodies of the present invention having specificity for human CCR5 or a portion thereof, can block binding of a chemokine (e.g., RANTES, MIP-1α, MIP-1β) to the receptor and inhibit function associated with binding of the chemokine to the receptor. In one embodiment, the antibody is monoclonal antibody 5C7 or a monoclonal antibody (mAb) which can compete with 5C7 for binding to human CCR5 or portion of human CCR5. In another embodiment, the antibody is monoclonal antibody 2D7 or a mAb which can compete with 2D7 for binding to human CCR5 or portion of human CCR5." (emphasis added)

In fact, the specification teaches that the monoclonal anti-CCR5 antibody 5C7 reacted only with chimeras that contained the amino-terminal region of CCR5, not the second extracellular loop (see page 61, lines 20-29; and Example 1, and Wu *et al., J. Exp. Med., 186*:1373-1381 (1997), and Figure 7). In other words, the antibody 5C7 does not bind "to the second extracellular loop of a human chemokine receptor 5 (CCR5)", as required in the pending claims.

In addition, Applicants respectfully point out that the specification teaches that antibody 5C7 was not able to block the binding of CCR5 ligands RANTES, MIP-1α or MIP-1β to CCR5 (see page 62, lines 8-12; and Example 1, and Wu *et al.*, *J. Exp. Med., 186*:1373-1381 (1997)). In other words, the antibody 5C7 does not "inhibit binding of a chemokine to the receptor, wherein said chemokine is MIP-1α, MIP-1β, or RANTES", as required in the pending claims.

Therefore, the Examiner's characterization of 5C7 as binding the second extracellular loop of CCR5 is incorrect. Also, the instant specification teaches the opposite: that 5C7 does not bind the second extracellular loop of CCR5, and furthermore 5C7 does not inhibit chemokine ligands binding to CCR5.

Thus, the 5C7 antibody disclosed in Bleul et al. does not incorporate all of the limitations of the claimed antibodies, and therefore Bleul et al. does not teach or suggest all of the limitations of the instant claims. As such, Bleul et al. cannot anticipate the claimed invention. Applicants respectfully request reconsideration and withdrawal of the rejection of claims 158, 160, 179, 181, 200 and 202 under 35 U.S.C. §102.

The Rejections of Claims 158, 160, 179, 181, 200 and 202 under 35 U.S.C. §103 Should Be Withdrawn

A. The Examiner rejected claims 158, 160-161, 163, 179, 181-182, 184, 200, 202-203, and 205 under 35 U.S.C. §103(a) as being unpatentable over Bleul et al. (March 1997 PNAS 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997.

The Examiner argued that the reasons why claims are anticipated by Bleul are as set forth in the §102 rejection. The Examiner stated that Bleul et al. does not teach chimeric antibodies as in claims 161, 182, and 203, or humanized antibodies as in claims 163, 184, and 205. The Examiner took the position that, "It would have been obvious to one of ordinary skill in the art to modify the antibody of Bleul by humanizing it as taught by Hoxie, thereby arriving at the invention of claims 161, 163, 182, 184, 203 and 205."

As explained above, the 5C7 antibody which Bleul et al. describes does not bind the second extracellular loop of CCR5 and does not inhibit binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. 5C7 binds to the amino terminal portion of CCR5.

Therefore, merely humanizing the 5C7 antibody disclosed in Bleul et al. would not reverse these characteristics and make it capable of binding the second extracellular loop of CCR5 and inhibiting binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. Contrary to the Examiner's assertion, one of skill in the art, modifying the

5C7 antibody disclosed in Bleul et al. by humanizing it allegedly as according to Hoxie et al., would not arrive at the claimed antibodies, which do inhibit binding of chemokines to CCR5, and which do bind the second extracellular loop of CCR5.

B. The Examiner rejected claims 158, 160-161, 163, 166, 179, 181-182, 184, 187, 200, 202-203, 205, and 208 under 35 U.S.C. §103(a) as being unpatentable over Bleul et al. (March 1997 PNAS 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997, and further in view of Rodwell (U.S. Patent 4,671,958).

The Examiner argued that the reasons why claims are anticipated by Bleul are as set forth in the §102 rejection. The Examiner stated that neither Bleul et al. nor Hoxie et al. teaches Fab and (Fab')2 fragments of antibodies. The Examiner took the position that, "It would have been obvious to one of ordinary skill in the art to modify the [antibody] of Bleul by making Fab or (Fab')2 fragments, as taught by Rodwell."

As explained above, the 5C7 antibody which Bleul et al. describes does not bind the second extracellular loop of CCR5 and does not inhibit binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. 5C7 binds to the amino terminal portion of CCR5.

Therefore, making Fab or (Fab')2 fragments of the 5C7 antibody disclosed in Bleul et al. would not reverse these characteristics and make it capable of binding the second extracellular loop of CCR5 and inhibiting binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. Contrary to the Examiner's assertion, one of skill in the art, modifying the 5C7 antibody disclosed by Bleul et al. by making Fab or (Fab')2 fragments, as allegedly taught by Rodwell, would not arrive at the claimed antibodies, which do inhibit binding of chemokines to CCR5, and which do bind the second extracellular loop of CCR5.

C. The Examiner rejected claims 158, 160-163, 179, 181-184, 200, and 202-205 under 35 U.S.C. §103(a) as being unpatentable over Bleul et al. (March 1997 PNAS 94:1925-1930) in view of Hoxie (U.S. Patent 5,994,515) and as evidenced by Information for Authors for Proceedings of the National Academy of Sciences USA, January 1997, and further in view of Osband (U.S. Patent 4,716,111).

The Examiner argued that the reasons why claims are anticipated by Bleul are as set forth in the §102 rejection. The Examiner stated that neither Bleul et al. nor Hoxie et al. teaches methods of making human antibodies. The Examiner took the position that, "It would have been obvious to one of ordinary skill in the art to modify the [antibody] of Bleul by making Fab or (Fab')2 fragments, as taught by

Osband." For clarity, it appears that the Examiner perhaps meant to say "modify the [antibody] of Bleul by making human antibodies, as taught by Osband."

As explained above, the 5C7 antibody which Bleul et al. describes does not bind the second extracellular loop of CCR5 and does not inhibit binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. 5C7 binds to the amino terminal portion of CCR5.

Therefore, making human antibodies of the 5C7 antibody disclosed in Bleul et al. would not reverse these characteristics and make it capable of binding the second extracellular loop of CCR5 and inhibiting binding of a chemokine to CCR5, wherein the chemokine is selected from the group consisting of MIP-1α, MIP-1β, and RANTES. Contrary to the Examiner's assertion, one of skill in the art, modifying the 5C7 antibody disclosed by Bleul et al. by making human antibodies, as allegedly taught by Osband, would not arrive at the claimed antibodies, which do inhibit binding of chemokines to CCR5, and which do bind the second extracellular loop of CCR5.

Applicants submit that Bleul et al. does not teach or suggest all of the limitations of the instant claims, and Hoxie et al., Rodwell et al., and Osband et al. all fail to remedy the deficiencies in Bleul et al. Furthermore, the references relied upon (Bleul et al., Hoxie et al., Rodwell et al., and Osband et al.) do not put the public in possession of the claimed antibodies, i.e., the resulting combination suggested by the Examiner (e.g. humanized 5C7, fragments of 5C7, and human 5C7) is not the claimed invention because it would not bind the second extracellular loop of CCR5 and would not inhibit chemokine binding to CCR5.

Thus, the presently claimed invention is non-obvious over the cumulative reference teachings of the art cited by the Examiner.

Therefore, Applicants respectfully request reconsideration and withdrawal of these rejections of claims under 35 USC §103(a).

MAINTAINED REJECTIONS

Double Patenting

Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 were rejected by the Examiner under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-36 of U.S. Patent No. 6,528,625. Specifically, the Examiner argued that the "Although the conflicting claims are not identical, they are not patentably distinct from each other

because the claims in the instant case are generic with respect to antibody whereas the claims in the '625 patent name specific monoclonal antibodies which are within the scope of the instant claims. The issued claims would anticipate the instant claims."

Applicants respectfully traverse the rejection and consider that the obviousness-type double patenting rejection is improper, however in an effort to expedite prosecution, and in no way acquiescing to the Examiner's rejections, Applicants submit herewith a Terminal Disclaimer to obviate the obviousness-type double patenting rejection over U.S. Patent No. 6,528,625.

Therefore, Applicants respectfully request reconsideration and withdrawal of the obviousness-type double patenting rejection over claims 1-36 of U.S. Patent 6,528,625.

The Rejection of Claims under 35 USC §103(a) Should Be Withdrawn

Claims 158, 160-163, 166, 179, 181-184, 187, 200, 202-205, and 208 were rejected by the Examiner under 35 U.S.C. §103(a) as unpatentable over Li et al. (U.S. Patent 6,025,154), in view of Li et al. (U.S. Patent 6,759,519), Raport et al. (*J. Biol. Chem.*, 271(29):17161-17166, 1996), Combadiere et al. (*J Leukocyte Biol.*, 60:147-152, 1996), Samson et al. 1996 (*Biochemistry*, 35:3362-3367, 1996), and Atchison et al. (*Science*, 274 :1924-1926, 1996), as evidenced by Wu et al. (*J. Exp. Med.* 186(8):1373-1381, 1997), and Samson et al. 1997 (*J. Biol. Chem.*, 272(40): 24934-24941, Oct. 1997).

Applicants remarks and arguments are as follows:

1. There was no teaching, suggestion, or motivation to combine references cited or to modify the reference in Li et al. to make an antibody to CCR5 which combined the characteristics of (i) inhibiting chemokine binding to CCR5 and (ii) inhibiting HIV infection.

    a. The Examiner's asserted motivation is stated on page 11 of the November 16, 2007 Office Action: "It would have been obvious to one of ordinary skill in the art to modify the methdods of Li who teaches making antibodies against the extracellular domains of CCR5 and selecting those that inhibit ligand binding, to select those that inhibit binding of MIP-1α, MIP-1β, or RANTES and HIV entry, with a reasonable expectation of success. The motivation to do so would be to make an antibody that can inhibit HIV entry, which could be useful as an therapeutic for HIV". However, anti-CCR5 antibodies that block HIV were already known at the time of filing – therefore, Applicants submit that there would not have been any motivation for one of skill in the

art to seek an antibody containing the claimed characteristics, i.e., an antibody capable binding CCR5, inhibiting chemokine binding to CCR5, and blocking HIV infection.

i. For example, Wu et al. May 1997 (May 5, 1997; J. Exp. Med. 185(9):1681-1691; IDS Reference no: AT4) described a monoclonal antibody (3A9) that binds to CCR5 and inhibits M-tropic HIV infection of cells (see pages 1686-1687, and Figure 6). (Incidentally, 3A9 was unable to block chemokine binding to CCR5, despite being the most effective inhibitor of M-tropic HIV infection). Thus, Wu et al. May 1997 supports the conclusion that antibodies which blocked HIV infection already existed and were known to one of ordinary skill in the art. Applicants submit that Wu et al. May 1997 supports the argument that there would not have been any motivation for one of skill in the art to seek an antibody containing the combination of claimed characteristics.

b. As previously argued in Applicants' response dated August 29, 2007, Atchison et al., teaches away from combining antibodies that block HIV infection and inhibit chemokine binding. As discussed below, Rucker et al. also teaches away from the combination.

i. Atchison et al. (December 13, 1995, Science 274:1924-1926; IDS Reference No: AZ5) teaches away from the combination because:

1. Atchison et al. does not teach or suggest that the second extracellular loop of CCR5 is important for HIV infection.
2. In addition, Atchison et al.:
   a) States that receptor chimeras containing the second extracellular loop of CCR5 "repeatedly had no coreceptor function" for HIV infection (page 1925, first column);
   b) States, "substitution of the NH2-terminal segment from CCR5 (5222) conferred robust susceptibility to HIV-1 cell entry" (Emphasis added; page 1925, first column).
   c) Indirectly indicates that an antibody that binds the NH2-terminal domain of CCR5 would be expected to inhibit HIV infection because the reference teaches that the "NH2-terminal segment [of CCR5] confers robust susceptibility to HIV-1 cell entry," but this is not the claimed invention.

Thus, Atchison et al. teaches away from the combination.

ii. Rucker et al. (Nov 1, 1996; Cell 87:437-446, submitted herewith as Supplemental IDS Ref No: BV) also teaches away from the combination.

1. Rucker et al., using chimeric CCR2b/CCR5 receptors, demonstrated that M-tropic HIV strains "required either the amino-terminal domain or the first extracellular loop of CCR5" (see abstract, and page 437, second column, last paragraph); Rucker stated that "the amino-terminal domain appears to play an important role in cofactor function as it is sufficient to confer M-tropic cofactor activity to CCR2b", and that "The amino-terminal domain of CCR5 was the only region that, when introduced into CCR2b, conferred M-tropic cofactor activity..." (see page 439, second column, first full paragraph, and page 443, first column, last paragraph).
2. In addition, Rucker et al. stated that "Introduction of the second extracellular loop from CCR5 into CCR2b failed to confer M-tropic cofactor function...Thus, the second loop appears to play little role in cofactor specificity..." (see page 444, first paragraph; emphasis added).
3. In general, Rucker et al. directs *toward* the N-terminus or 1st extracellular loop of CCR5, and *away* from the second extracellular loop, for blocking HIV binding.

Thus, Rucker et al. teaches away from an antibody to CCR5 which combined the characteristics of (i) inhibiting chemokine binding to CCR5 and (ii) inhibiting HIV infection.

2. There was no expectation of success in modifying the screen of Li et al. or combining the screen of Li et al. with the other references to generate an antibody to CCR5 which combined *both* the characteristics of (i) inhibiting chemokine binding to CCR5 and (ii) inhibiting HIV infection.

a. One of skill in the art at the time, reading that chemokine ligands of CCR5 block HIV infection, would not necessarily expect antibodies that block access of those chemokines to CCR5 to help block HIV.

i. Cocchi et al. (Dec 15, 1995; Science 270:1811-1815; IDS Reference No: AW2) identified RANTES, MIP-1α, and MIP-1β as "HIV-suppressive factors", stating that "chemokines can mediate antiviral effects..." (see page 1813, last paragraph); Cocchi et al. suggested using these chemokines to control HIV. Applicants submit that one of ordinary skill in the art in view of this would not

necessarily expect that an antibody which inhibits binding of MIP-1α, MIP-1β or RANTES to CCR5 would be useful or effective in blocking HIV infection.

b. One of skill in the art at the time would not have expected to succeed in making anti-CCR5 antibodies that inhibit *both* HIV infection and chemokine binding.

i. As described above, Atchison et al. and Rucker et al. teach away from an antibody which binds CCR5 containing the combined characteristics of blocking HIV infection and inhibiting chemokine binding to CCR5. Atchison et al. and Rucker et al. give one of ordinary skill in the art an expectation that such a combination is not reasonably possible to achieve.

ii. Samson et al. 1997 (Oct 3, 1997; JBC 272(40):24934-24941; cited by Examiner) later confirmed that the second extracellular loop of CCR5 is "critical for high affinity binding of MIP-1α, MIP-1β, and RANTES"; and the N-terminus and first extracellular loop "constitute the main regions conferring [HIV] co-receptor properties to CCR5" (see page 24939, first full paragraph; also page 24940, paragraph spanning first and second columns)

iii. Wu et al. Oct. 1997 (IDS Reference No: AS4) is a later publication of Applicants' own work regarding CCR5 antibodies of the invention. The Examiner is apparently using Applicants' own later publication to argue that one of skill in the art at the time would have had reasonable expectation of success in generating claimed antibodies of the instant invention. The Examiner is using Wu et al. Oct. 1997 to provide impermissible hindsight.

c. Rosckhe et al. (Oct. 30, 2004; 44th Annual Interscience Conference on Antimicrobial Agents and Chemotherapy; IDS Reference No: BU) also confirms and corroborates that antibodies to CCR5 which inhibit chemokine binding to CCR5 do not inherently also block HIV infection. Applicants believe that Roschke et al. is evidence that a skilled artisan screening antibodies for ability to inhibit chemokine binding to CCR5 would not inevitably succeed in generating antibodies that also block HIV infection.

3. In summary, the references as a whole

   a. Do not suggest desirability of making an antibody to CCR5 which combines the characteristics of (i) inhibiting chemokine binding to CCR5 and (ii) inhibiting HIV infection.

   b. Do not render obvious anti-CCR5 antibodies having the combined characteristics of inhibiting HIV infection and inhibiting chemokine binding to CCR5.

   c. Do not give one of skill in the art, at the time of filing, a reasonable expectation of success in making anti-CCR5 antibodies having the combined characteristics of inhibiting HIV infection and inhibiting chemokine binding to CCR5.

Accordingly, in absence of evidence to the contrary, Applicants assert that there is no credible scientific reasoning or evidence to support the Examiner's assertion that it would have been obvious to combine the screen of Li et al. to identify an antibody which binds CCR5 and inhibits chemokine binding to CCR5 with a further screen to identify antibodies which also block HIV infection. Applicants additionally assert that a skilled artisan would not have been expected to succeed in generating an antibody to CCR5 containing both attributes. Thus, the presently claimed invention is non-obvious over the cumulative reference teachings of the art cited by the Examiner.

Therefore, Applicants respectfully request reconsideration and withdrawal of this rejection of claims under 35 USC §103(a).

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CONCLUSION

In view of the remarks and amendments made herein, Applicants respectfully submit that the rejections presented by the Examiner are now overcome and that this application is in condition for allowance. Applicants earnestly invite the Examiner to call the undersigned at (617) 679-7166, in order to discuss the rejections of record and this response.

This paper is being filed timely as a request for three month extension is filed concurrently herewith. Applicants believe no further extensions of time are required. In the event any additional extensions of time are necessary, the undersigned hereby authorizes the requisite fees to be charged to Deposit Account No. 501668.

Entry of the remarks made herein is respectfully requested.

Respectfully submitted,

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MILLENNIUM PHARMACEUTICALS, INC.

By _____

Jonathan K. Hamm, Ph.D.
Registration No. 59,608
40 Landsdowne Street
Cambridge, MA 02139
Telephone - 617-679-7166
Facsimile - 617-551-8820